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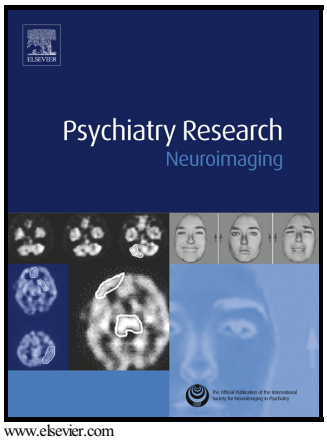

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Investigation of orbitofrontal sulcogyral pattern in chronic schizophrenia

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Running title: OFC sulcogyral pattern in chronic schizophrenia

Abstract

Abnormalities of orbitofrontal cortex (OFC) pattern type distribution have been associated with schizophrenia-spectrum disorders. We investigated OFC pattern type in a large sample of chronic schizophrenia patients and healthy controls. We found an increased frequency of Type II but no difference in Type I or III folding pattern in the schizophrenia group in comparison to controls. Further large studies are required to investigate the diagnostic specificity of altered OFC pattern type and to confirm the distribution of pattern type in the normal population.

Keywords: Orbitofrontal cortex, pattern type, schizophrenia

1. Introduction

The human orbitofrontal cortex (OFC) shows large individual variability in sulcogyral pattern. Despite this variability, Chiavaras and Petrides (2000) identified three major OFC sulcogyral patterns in the general population (Type I, Type II and Type III) based on variations of the typical 'H-shaped' sulcal pattern. Of these, Type I is the most common, followed by Type II then Type III. As cortical gyrification is completed shortly after birth (Chi et al., 1977), and is a relatively stable characteristic (Magnotta et al., 1999), OFC sulcogyral pattern has been proposed to represent a marker of early neurodevelopment (Nakamura et al., 2007).

Altered OFC sulcogyral pattern has been reported in schizophrenia-spectrum disorders. The most consistent finding has been decreased Type I pattern in the right hemisphere (Nakamura et al., 2007; Nakamura et al., 2008; Takayanagi et al., 2010; Bartholomeusz et al., 2013; Lavoie et al., 2014). In addition, increased Type II (Bartholomeusz et al., 2013; Lavoie et al., 2014) and III (Nakamura et al., 2007; Nakamura et al., 2008; Chakirova et al., 2010; Takayanagi et al., 2010) pattern in the right hemisphere has been reported in some but not all (Chakirova et al., 2010) cohorts. These findings suggest that Type I folding pattern may represent a resilience marker, whilst either Type II or Type III pattern may represent risk markers, for schizophrenia.

Given the discrepancies in the literature regarding the prevalence of Type II and III pattern types in the schizophrenia-spectrum disorders, the aim of this study was to investigate the distribution of OFC sulcogyral pattern in a large sample of individuals with chronic schizophrenia. We sought to determine whether Type I is reduced, and whether Type II or Type III pattern is increased, in schizophrenia patients compared to controls.

2. Methods

2.1 Participants

Data for the current study were taken from a previous study (Velakoulis et al., 2006). This consisted of 89 patients with chronic schizophrenia (duration of illness 13.4 ± 8.5 years) and 87 healthy controls with no personal or family history of psychiatric disorder. Patients had a diagnosis of schizophrenia according to DSM-III-R diagnostic criteria and were recruited from the North Western Mental Health Program in Melbourne, Australia. Controls were recruited from similar sociodemographic areas as the patients. All patients had at least 2 years of neuroleptic exposure at the time of scanning. Exclusion criteria for all participants included a history of serious head injury, neurological disorder, seizures, impaired thyroid function, corticosteroid use or alcohol/substance abuse or dependence according to the DSM-III-R. Seventy-two of the controls were from our previous study (Bartholomeusz et al., 2013), with an additional 14 recruited. Seven participants (6 patients and 1 control) were excluded because of poor MRI quality, leaving a total sample of 83 patients and 86 controls. The Melbourne Health Human Research and Ethics Committee approved this study. Written informed consent was obtained from all participants.

2.2 MRI Acquisition

Anatomical T1-weighted images were acquired on a 1.5-tesla Signa (GE Medical Systems, Milwaukee), resulting in 124 contiguous SPGR images (echo time = 3.3 ms; repetition time = 14.3 ms; flip angle = 30 degrees; matrix size = 256x256; field of view = 24 x 24 cm matrix; voxel dimensions = 0.938 x 0.938 x 1.5mm).

2.3 OFC Sulcogyral Pattern Classification

Classification of OFC pattern type was based on continuity among medial (MOS), lateral (LOS) and transverse (TOS) orbital sulci following the method of Chiavaras and Petrides (2000) and modified by Bartholomeusz et al., (2013), as previously described. Orbital sulci were traced in coronal and transverse planes in each hemisphere using Analyze 10.0 (Mayo Clinic), and visually inspected for classification into one of three types (Type I, II or III). Classification was performed

by a single rater (PW) blinded to diagnosis and sex. Inter-rater reliability (PW and CB) was performed on 40 hemispheres blind to group. The intraclass correlation coefficients (Cronbach's α) were 0.946 for the right hemisphere and 0.922 for the left hemisphere.

2.4 Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) v19.0. Group differences in pattern type distribution, asymmetry, handedness and sex were assessed with Pearson's χ^2 statistics. Independent t-tests were performed to assess group differences in age. To account for potential sex effects, analyses were also conducted separately for males and females.

3. Results

Schizophrenia patients were significantly older (35 vs 27 years, $p<0.0001$) and had a greater proportion of males (87% vs 64%, $p<0.001$) than control participants. Univariate analyses of variance showed no significant effect of age on OFC type (hemispheres analysed separately) or interaction between group and age.

There were no overall significant differences in the distribution of OFC type in each hemisphere between patients and controls (Table 1), although a trend existed for both hemispheres (right: $p=0.089$; left: $p=0.078$). Given this trend, we conducted post-hoc analyses for each type in each hemisphere separately. For the right hemisphere, Type II pattern was increased ($\chi^2(1)=4.7$, $p=0.04$) in patients compared to controls. For the left hemisphere, there were no significant group differences in each pattern type expression. Separate analyses performed for males and females showed no sex-specific effects on pattern type distribution. Left-right symmetry of OFC pattern type did not differ between patients and controls ($p=0.282$). Table 1 shows the distribution of OFC pattern type in the current and previous studies conducted to date.

4. Discussion

This study found a trend-level difference in the distribution of OFC pattern type in a large sample of chronic schizophrenia and healthy controls. In contrast to previous research, post-hoc analyses showed no difference in the expression of Type I and Type III folding pattern between diagnostic groups. However, consistent with our previous studies in first-episode psychosis (Bartholomeusz et al., 2013) and clinical at-risk individuals who transitioned to psychosis (Lavoie et al., 2014), we found an increased incidence of Type II pattern in the right hemisphere of schizophrenia patients. This finding of increased Type II raises the possibility that the Type II sulcogyral pattern may also be a morphological risk marker for psychotic disorders. Although the underlying mechanisms of this risk remain unknown, variation in Type II sulcogyral pattern may reflect a neurodevelopment aberration of possibly genetic or environmental origin (see Ganella et al., 2015).

Our findings suggest that any difference in the distribution of OFC sulcogyral pattern is likely to be subtle. Although our sample was large there were no overall effects and our posthoc analysis of increased Type II just met significance. Our finding of increased Type II but no change in Type I or III is discrepant with most of the schizophrenia-spectrum research. The reason for this discrepancy is unclear. However, deviation in the distribution of OFC pattern type amongst our control sample from previous controls may have contributed to our result. Our controls had a lower incidence of Type II and higher incidence of Type III in the right hemisphere compared to that reported by Chiavaras and Petrides (2000; see Table 1). In contrast, OFC distribution in the right hemisphere of our patient sample was similar to a previous sample of individuals with chronic schizophrenia (Nakamura et al., 2007). This suggests that the unusually low rate of Type II and high rate of Type III in our control sample contributed to our group difference, or lack thereof, in Type II and Type III folding pattern, respectively. A limitation of this study is that our control sample included those from our previous study (Bartholomeusz et al., 2013). Nevertheless, of the subset

that was independent (n=14), the frequency of OFC pattern type in the right hemisphere was similar to our wider sample (Type I>Type III>Type II) and diagnostic comparisons also yielded trend-level findings for increased right side Type II pattern in schizophrenia.

The discrepancy in OFC pattern distribution between control cohorts might be explained by sample size, prenatal factors, socioeconomic status, temperament, and cognitive function, some which have previously been linked to the Type III pattern (Nakamura et al., 2007; Whittle et al., 2014). Variation in brain morphology according to geographical location (Bakken et al., 2011) may have also accounted for the unusual pattern distribution in our southern hemisphere control sample. Given that OFC classification is a complex technique it is also possible that there are discrepancies between studies in the method of classification that may have accounted for the different results. Although all studies have followed the general method of Chiavaras and Petrides (2000), slight variations may exist due to, for example, the use of different imaging software, method used for excluding images with movement artefacts, the plane in which sulci were marked, and whether sulci or the grey matter within the sulci was marked/traced. Further, our group found that it was necessary to introduce additional guidelines to aid in classification (e.g. in how sulci were defined (see Bartholomeusz et al., 2013 for discussion). This was also partially due to the discovery of anomalies in OFC patterns that were not previously reported (e.g. MOS intact but disconnected from the TOS). The method of classification of Type III has also been shown to vary between research laboratories in rare instances where the LOS but not MOS is disconnected; One study (Chakirova et al., 2010) classified these rare patterns as a new "Type IV" while our laboratory classified these patterns as Type III (given that a disconnected LOS is the distinguishing feature of the Type III pattern). Despite these modest differences in methodology, the distribution of OFC type in our schizophrenia sample was similar to previous schizophrenia cohorts (Nakamura et al., 2007; Nakamura et al., 2008), thus it is unlikely that discrepancies in classification accounted for our results. Nevertheless, reliability of OFC classification across laboratories should be determined.

Despite evidence for reduced Type I, and increased Type III pattern in psychosis populations, there is variability in the literature. Such variability is not surprising given the small samples of past research as well as the clinical heterogeneity of schizophrenia. As such, further studies investigating OFC pattern type in large samples of participants across different ethnic and demographic groups is warranted. Studies are also required to determine the diagnostic or behavioral specificity of altered OFC pattern type, the stability of OFC pattern type over time and the distribution of folding pattern in the normal population.

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Contributors

Authors CP and CB designed the study. Author PW and CB performed the OFC sulcogyral classifications. Author VC carried out the statistical analyses. Author VC wrote the first draft of the manuscript. All authors contributed to and have approved the manuscript.

Conflict of interest

There are no competing financial interests in relation to the work described in this paper. All authors declare that they have no conflicts of interest.

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Highlights

- This study investigated OFC pattern type in a large sample of chronic schizophrenia patients and healthy controls
- We found an increased frequency of Type II but no difference in Type I or III folding pattern in the schizophrenia group in comparison to controls
- Our study suggests that further large studies are required to investigate the diagnostic specificity of altered OFC pattern type and to confirm the distribution of pattern type in the normal population

Table 1. Distribution of OFC sulcogyral pattern type in psychosis

Current Study	Chiavaras &	Nakamura et al (2007)	Chakirova et al	Takayanagi et al	Bartholomeusz et al	Lavoie et al (2014)

					Petrides (2000)				(2010)		(2010)		(2013)			
	Chronic % (n)	HC % (n)	χ^2	p [a]	HC % (n)	Chronic % (n)	HC % (n)	FEP % (n)	HC % (n)	FEP % (n)	HC % (n)	FEP % (n)	UHR-P % (n)	UHR-NP % (n)	HC % (n)
Right Hemisphere			4.87	0.089											
Type I	48 (40)	55 (47)			64 (32)	42 (21)	62 (31)	44 (15)	61 (22)	31 (13)	57 (20)	45 (43)	22 (11)	48 (37)	67 (39)
Type II	29 (24)	15 (13)*			26 (13)	34 (17)	28 (14)	18 (6)	22 (8)	38 (16)	34 (12)	28 (27)	35 (17)	23 (18)	8.6 (5)
Type III	23 (19)	30 (26)			10 (5)	24 (12)	10 (5)	32 (11)	11 (4)	31 (13)	9 (3)	27 (26)	43 (21)	29 (22)	24 (14)
Left Hemisphere			5.12	0.078											
Type I	58 (48)	58 (50)			48 (24)	40 (20)	46 (23)	41 (14)	53 (19)	48 (20)	51 (18)	48 (46)	43 (21)	52 (40)	43 (33)
Type II	14 (12)	26 (22)			34 (17)	34 (17)	36 (18)	27 (9)	25 (9)	31 (13)	31 (11)	25 (24)	33 (16)	16 (12)	27 (9)
Type III	28 (23)	16 (14)			18 (9)	26 (13)	18 (9)	29 (10)	19 (7)	21 (9)	17 (6)	27 (26)	25 (12)	33 (25)	30 (16)

Note: [a]Analyses of the group comparison between the current chronic schizophrenia and healthy control sample.
*significance at $p < 0.05$.
Chronic, chronic schizophrenia; HC, healthy controls; FEP, first-episode psychosis; UHR-P, ultra high risk individuals who later transitioned to psychosis; UHR-NP, ultra high risk individuals who did not transition to psychosis